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Harvard Law School
Third Year Written Requirement

FDA Premarket Regulation of Tissue-Engineered Replacement Parts for Humans

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Many plants and some animals have the marvelous ability to regenerate damaged or lost tissues and organs. For example, certain lower animals, including starfish, can regenerate entire missing body parts.¹ Imagine an oysterman concerned about starfish predating on his daily oyster haul. To remedy the problem of starfish diminishing the local oyster population, he decides to cut the predators into pieces during his dives. Time passes by and the oysterman continues engaged in this practice. Despite all his efforts, the starfish population continues multiplying. Therefore, the oysterman starts searching for an answer to his problem. Much to his surprise, he discovers that he is contributing to the increase in the starfish population. Each one of the starfish pieces he threw into the water has the potential to regenerate its missing parts and gave rise to a new starfish.

By sharp contrast, humans are much more limited in their ability to regenerate and heal. We are able to regenerate tissues such as skin and liver, but only to a certain extent. Moreover, these capabilities may be lost or diminished with certain diseases. The most severe cases of improper healing may give rise to serious complications and sometimes result in amputation or death.

Our limited ability to regenerate and heal has prompted the creation of a vast array of inventive solutions, including the replacement of tissues and organs with artificial parts. Examples of successful, non-biological or artificial replacement parts include dentures, hearing aides, artificial limbs, and pacemakers. These products have saved millions of lives and improved the quality of life of others. Nevertheless, replacement of living tissue with non-biological parts may lead to unwanted consequences, such as complications arising from blood/material interactions. Although some compact artificial devices serving specialized functions have excellent long-term reliability, many devices cannot perform all of the functions of a single organ and therefore cannot prevent progressive patient deterioration. Still other medical devices are so complicated

¹Additionally, some amphibians can regenerate missing limbs, jaws, tails, retina and lens. See Shin Tochinai, *What do we learn from regeneration in lower animals?* in TISSUE ENGINEERING FOR THERAPEUTIC USE 4 (Yoshito Ikada, ed. 1999) at 141-151.

and expensive- such as a dialysis or a heart-lung machine- that it is impossible for patients to afford them or to have them in home.

More recently, doctors have resorted to transplantation as a means to replacing missing or damaged tissues and organs. Transplantation involves grafting living tissue or organs from other humans (allografts) and animals (xenografts) in order to restore lost or impaired biological functions. The era of solid organ transplantation began in 1954, with the first successful kidney transplant between identical twins.² Modern techniques result in successful transplants that eliminate many of the shortcomings associated with non-biological replacement parts. Unfortunately, the high demand for human organs outnumbers current supplies. For example, there are 81,332 patients waiting for an organ transplant in the United Network for Organ Sharing (UNOS) waitlist.³ Xenografts are used as alternatives to human organs, but “substantial scientific and immunologic hurdles currently limit their use.”⁴

The scarcity of human organs available for transplant is exacerbated by ethical, moral and religious concerns. In addition, organs have relatively short life span once they are harvested, and transmit certain diseases from donor to recipient. Additionally, once an organ transplant is performed, biological differences between the donor and the recipient may lead to its rejection or other unwanted secondary effects. For example, a couple of months ago a seventeen year-old girl suffered irreversible brain damage and ultimately died after mistakenly received a heart and lung transplant from a donor with a different blood type at Duke University Hospital.⁵

The shortcomings related to conventional replacement parts for humans have prompted the search and development of alternatives, including the engineering of tissues and organs in the laboratory. This practice, known as “tissue engineering,” is “an interdisciplinary field that applies the principles of engineering and

²Laura E. Niklason and Robert Langer, *Prospects for Organ and Tissue Replacement*, 285(5) JAMA 573, 574 (2001) (citing J. E. Murray et al., *Renal Transplantation: a Twenty-Five Year Experience*, 184 ANN. SURG. 565 (1976)).

³United Network for Organ Sharing (UNOS), <http://www.unos.org>.

⁴Niklason, *supra* note 2.

⁵*Organ Finder Admits Missing Blood Type*, NY Times, March 17, 2003 at A18.

the life sciences toward the development of biological substitutes that restore, maintain, or improve tissue function.”⁶ The main goal in this field is to design living tissues that can meet the needs of each individual patient.⁷

Among many other parties, the military is showing interest and support for tissue engineering by funding medical applications for tissue-engineered products and biomaterials.⁸ According to a study about the growth of this industry, “at the beginning of 2001 tissue engineering research and development was being pursued by over three thousand scientists and support staff in more than seventy startup companies or business units with a combined annual expenditure of over \$600 million.”⁹ This study found that the aggregate investment in tissue engineering firms since 1990 exceeds \$3.5 billion; that the industry has “more than doubled in size since 1995,” and that it “remains a dynamic and growing private sector, premarket enterprise.”¹⁰ However, because tissue-engineering is still in its infancy, there is widespread uncertainty about the regulatory process for bringing these products into the United States market.

The Food and Drug Administration (FDA) is the agency responsible for the regulation of medical products in the United States. FDA is currently structured to regulate medical products under the separate categories of devices, biologics and drugs. However, advances in medical technologies such as tissue engineering have resulted in the development of products that combine two or more components belonging to separate categories. Because these “combination products” do not fall within the statutory boundaries of a specific category, their premarket regulation is currently a challenge for the agency. According to a notice published in the Federal Register, “[n]ew technologies and products that result from the combination of components that would otherwise be regulated under different regulatory authorities raise not only unique scientific ques-

⁶Robert Langer and Joseph P. Vacanti, *Tissue Engineering*, 260 SCI. 920 (1993).

⁷Joseph P. Vacanti and Robert Langer, *Tissue Engineering: the Design and Fabrication of Living Replacement Devices for Surgical Reconstruction and Transplantation*, (suppl. I) LANCET 31, 32 (1999).

⁸For example, Advanced Tissue Sciences, Inc. had part of its clinical trial for the treatment of chemical burns with its tissue-engineered skin (Dermagraft-TC) funded by the U.S. Army Institute of Chemical Defense. *Advanced Tissue Sciences Announces Funding of Dermagraft-TC™ Pre-Clinical Trial by the U.S. Army*, PR NEWswire, March 6, 1995.

⁹Lysaght, Michael J., and Joyce Reyes, *The Growth of Tissue Engineering*, 7 TISSUE ENG'G 485, 485 (2001).

¹⁰*Id.* at 487 and 490.

tions, but also regulatory challenges related to where and how such products should be regulated in order to ensure adequate and consistent regulatory oversight.¹¹ This paper is a description of tissue-engineered products, their potential for replacing conventional approaches to missing or failing tissues and organs, and FDA’s ongoing efforts to develop a comprehensive and uniform scheme for regulating them.

II. FDA Premarket Regulation of Medical Products

In the United States, the Food and Drug Administration (FDA) regulates medical products under the authority conferred by the federal Food, Drug and Cosmetic Act (FD&CA)¹² and the Public Health Service Act (PHSA)¹³. The agency regulates these products under the separate categories of devices, biologics, drugs and combination products. A “device” is defined as:

an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is... (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease... or (3) intended to affect the structure or any function of the body... *and which does not* achieve its primary intended purposes through chemical action within or on the body... *and which is not* dependent upon being metabolized for the achievement of its primary intended purposes.¹⁴

The PHSA defines a “biological product” as a “virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product... applicable to the prevention, treatment, or cure of a disease or condition of human beings.”¹⁵ The term “drug,” as defined by the FD&CA, includes “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and... articles (other than food) intended to affect the structure or any function of the body.”¹⁶ As discussed below, a combination product consists of two or more FDA-regulated components belonging to separate categories (e.g., drug/device, biologic/device, drug/biologic, or drug/device/biologic).

¹¹FDA Regulation of Combination Products; Public Hearing, 67 Fed Reg. 65802 (Oct. 28, 2002).

¹²Pub. L. No. 75-717, 51 Stat. 1040 (1938) (codified as amended 21 U.S.C.A §§ 301-399 (West 2003)).

¹³Ch. 288, 37 Stat. 309 (1912) (codified at 42 U.S.C.A. §§ 201-300 (West 2003)).

¹⁵42 U.S.C.A. § 262(i) (West 2003).

¹⁶21 U.S.C.A. § 321(g)(1) (2003).

Once a product is categorized as a biological product, drug, or device, it is respectively assigned to one of three divisions or centers: the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), or the Center for Devices and Radiological Health (CDRH). The Center to which a product is assigned retains the primary regulatory responsibilities and oversight over the product

CBER has regulatory authority over biological products, including blood and blood components, biological therapeutic products, vaccines, cellular ad gene therapies and allergenic products.¹⁷ Additionally, CBER regulates those medical devices that are intimately associated with blood collection and processing procedures as well as cellular therapies.¹⁸ CDRH is responsible for ensuring the “safety and effectiveness” of devices marketed in the U.S. and eliminating unnecessary human exposure to man-made radiation from medical, occupational and consumer products.¹⁹ CDRH also has jurisdiction over most medical devices except the “biological” devices regulated by CBER. Finally, CDER “has the regulatory responsibility for ensuring both the safety and effectiveness of all drugs that are intended for use by humans” except for the “biological” drugs regulated by CBER, and certain combination products and cosmoceuticals.²⁰

A. Product Classification

The sponsor of a medical product “may submit a request to the [FDA] respecting the classification of the product as a drug, biological product, device, or a combination product...or respecting the [Center] that will regulate the product.”²¹ The agency has 60 days after receipt of this request to determine the category of the product, confer jurisdiction over the product to a particular center, and “provide to the [sponsor] a

¹⁷See <http://www.fda.gov/cber>.

¹⁸*Id.*

¹⁹SUZANNE PARISIAN, FDA INSIDE & OUT 333 (Fast Horse Press ed., 2001).

²⁰*Id.* 145.

²¹21 U.S.C.A. § 360bbb-2(a) (West 2003).

written statement that identifies such classification... and the reasons for such determination.”²²

If the agency fails to provide this statement within the proscribed 60-day period, “the recommendation made by the [sponsor]... shall be considered to be a final determination... and may not be modified... except with the written consent of the person, or for public health reasons based on scientific evidence.”²³ With respect to combination products, FDA has created intercenter agreements among CBER, CDER, and CDRH that provide jurisdictional guidelines for their classification and regulation.

1. Combination Products

Because FDA is structured to regulate drugs, devices and biologics as separate categories, cutting edge technologies such as tissue engineering raise unique regulatory challenges.²⁴ More often than not, products developed through these technologies do not fit within the boundaries of the statutory definition of drugs, biologics, or devices, because they are usually comprised by at least two distinct components belonging to separate categories.²⁵ “From the time of enactment of the Medical Device Amendments of 1976 through 1990, there was no framework within FDA for deciding which Center of the agency would have jurisdiction over innovative products that did not fit clearly within statutory definitions of drug, biologic, or device.”²⁶ FDA currently regulates these products under the category of “combination products.”

The statutory definition of combination products includes the following:

²²21 U.S.C.A. § 360bbb-2(b) (West 2003).

²³21 U.S.C.A. § 360bbb-2(c) (West 2003).

²⁴“[FDA] recognizes that it may need to modify existing paradigms to address the unique characteristics of these combinations.” 67 Fed. Reg. 34722 (May 15, 2002).

²⁵“Most tissue-engineered constructs are composed of at least two important components: a group of cells, and a material scaffold on which they can grow.” Lawrence J. Bonassar and Charles A. Vacanti, *Tissue Engineering, the First Decade and Beyond*, 30/31 J. CELL’R BIOCHEM SUPP 297, 299 (1998).

²⁶HOW TO WORK WITH THE FDA: TIPS FROM THE EXPERTS 191 (Wayne L. Pines ed., 2000).

- (1) A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity;
- (2) Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;
- (3) A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or
- (4) Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.²⁷

According to this definition, combination products include not only products in which attributes of drugs, biologics, and/or device are incorporated into one entity, but also include products comprised of individual, discretely-identifiable entities that, considered alone, could be a drug, biologic, or device. Examples of device/biologic combination products include cellular and tissue implants, infused or encapsulated cells, heart valves; and cardiac, neural, and neuromuscular stimulation devices.

Congress first acknowledged the need for specific regulation on combination products in the Safe Medical Devices Act of 1990 (SMDA), which created intercenter agreements among CBER, CDER and CDRH.²⁸ According to recent federal House Reports, combination products “presently do not receive appropriate attention” within FDA, and “under current law, the FDA staff identifies which center within the agency should take the lead in reviewing combination products, but it does nothing further to track or facilitate review of such products.”²⁹

FDA has recognized that uncertainties about the regulatory requirements of combination products may cause

²⁸Safe Medical Devices Act of 1990, Pub. L. No. 101-629, section 16(a), 104 Stat. 4511, 4526 (codified as amended at 21 U.S.C. § 353 (West 2003)) (requiring the development of intercenter agreements to regulate products that constitute a combination of a drug, device, or biologic); and 21 C.F.R. § 3.4 (2003) (summarizing Intercenter Agreements).

²⁹H.R. Rep. No. 107-802 at 114 (2003), and H.R. Rep. No. 107-728(II) at 6 (2002).

delays in their development and marketing, and has initiated a process for clarifying these requirements.³⁰ Additionally, the agency has acknowledged the “need to develop policies and procedures that will ensure the efficient and effective review and regulation of combination products.”³¹ A notice published in the Federal Register enumerates a series of criticisms regarding the agency’s regulation of combination products, including:

concerns about the consistency, predictability, and transparency of the assignment process; issues related to the management of the review process when two (or more) FDA Centers have review responsibilities for a combination product; lack of clarity about the post-market regulatory controls applicable to combination products; and the lack of clarity regarding certain agency policies, such as when applications to more than one agency component are needed.³²

Because the category to which a combination product belongs is not always apparent, FDA drafted three Intercenter Agreements among CBER, CDER and CDRH, in order to provide guidance in the designation of combination products to a particular center. The agency is statutorily required to designate the Center with primary jurisdiction for the premarket review and regulation of a combination product based on the product’s “primary mode of action.”³³ The Intercenter Agreement between CBER and CDRH was drafted in October, 1991 to ensure that the manufacturer of a device/biologic combination product is required to submit only one application for premarket review.³⁴ Nevertheless, the jurisdiction of a particular center does not preclude consultations by that center with other agency centers “or, in appropriate cases, the requirement. . . of separate applications.”³⁵

Last year, FDA established a Combination Products Program within the Office of the Ombudsman, and a new Office of Combination Products (OCP) within the Office of the Commissioner, as required by MDUFMA.³⁶

The Congressional Budget Office estimated that the costs of creating this office would be “less than \$1

³⁰Combination Products Containing Live Cellular Components; Public Hearing, 67 Fed. Reg. 34722 (May 15, 2002).

³¹PARISIAN, *supra* note 19.

³³21 C.F.R. § 3.4(a) (West 2003).

³⁴PARISIAN, *supra* note 19 at 545.

³⁵21 C.F.R. § 3.4(b) (West 2003).

³⁶*FDA Establishes New Office of Combination Products*, FDA NEWS, Dec. 31, 2002 available at <http://www.fda.gov>.

million in 2003 and about \$4 million over the 2003-2007 period”, assuming that “more staff would be needed in the first two years to establish the data tracking systems and procedures of the new office.”³⁷ The statutorily mandated functions of the OCP are to ensure “the prompt assignment of combination products” to the agency center with primary jurisdiction, the “timely and effective premarket review of such products, and [the] consistent and appropriate post-market regulation of like products subject to the same statutory requirements...”³⁸ Additionally, the OCP must consult with stakeholders and the directors of FDA centers to determine if previous agreements or practices specific to the assignment of combination products to agency centers are consistent with the above requirements.³⁹ After such determination, the OCP has the authority to “determine whether to continue in effect, modify, revise, or eliminate such agreement, guidance or practice” and must publish any changes in the Federal Register.⁴⁰ Finally, OCP will assume and continue the functions of the Combination Products Program established earlier in 2002 within the Office of the Ombudsman and will work with the CBER, CDER and CDRH to develop guidance and/or regulations to clarify the agency’s regulation of combination products. In November, 2002 FDA held a “public hearing to discuss the assignment, premarket review, and postmarket regulation of combination products.”⁴¹

III. Overview of FDA Premarket Regulation for Conventional Replacement Parts⁴²

According to FDA’s current regulatory structure, conventional replacement parts fall within the categories of medical devices or biologics. Under the FD&CA, the manufacturer of a medical device must demonstrate that the product is safe, effective, properly designed, and adequately labeled.⁴³ Under FDA’s regulatory scheme, these products are further divided into Class I, Class II, and Class III devices, depending on the potential risks associated with them.⁴⁴

³⁷H.R. Rep. No. 107-728(II), *supra* note 29 at 6.

³⁸21 U.S.C.A. § 353(g)(4) (West 2003).

³⁹21 U.S.C.A. § 353(F) (West 2003).

⁴⁰*Id.*

⁴¹67 Fed Reg. 65801 *supra* note 11.

⁴²This section is only a brief introduction to FDA’s premarket regulation of devices and biologics.

⁴³21 U.S.C.A. § 360e (West 2003).

⁴⁴21 U.S.C.A. § 360c (West 2003).

Medical devices may be introduced to the market after either a premarket clearance by means of a 510(k) notification or a premarket approval through a “Pre-Market Application” (PMA) or Product Development Protocol (PDP) submissions.⁴⁵ A 510(k) notification is the “easiest way to get into the market.”⁴⁶ Most 510(k) applications do not require clinical study data, which typically consumes the great majority of a manufacturer’s resources.⁴⁷ However, in order to gain premarket approval with a 510(k), the sponsor needs to show that his device is “substantially equivalent to a device already in the market.”⁴⁸ The sponsor of a Class III device (i.e., devices which present “a potential unreasonable risk of illness or injury”)⁴⁹ must seek premarket approval through the PMA or PDP process. Both of these processes involve preclinical studies and clinical trials to demonstrate that the device is safe and effective.⁵⁰

In order to obtain premarket approval for a medical device or a biological product, FDA permits the limited distribution of medical products for use in clinical studies on humans. By statute, these clinical studies must be reviewed and approved by the human subject protection entity (the Institutional Review Board) of the institution performing them⁵¹ Additionally, the clinical study is subject to FDA approval of either an Investigational Device Exemption (IDE)⁵² for medical devices or an Investigational New Drug exemption (IND)⁵³ for drugs and biologics.⁵⁴ Although the requirements for IND and IDE applications are somewhat

⁴⁵David Smith, *Legal and Regulatory Issues* in WTEC Panel on Tissue Engineering 87 (Research International Technology Research Institute, World Technology (WTEC) Division, 2002).

⁴⁶Symposium, *Regulatory and Liability Considerations*, 6 B. U. J. SCI. & TECH. 5, para. 11 (2002).

⁴⁷Anne Marie Murphy. *The Biomaterials Access Assurance Act of 1998 and Supplier Liability: Who You Gonna Sue?*, 25 DEL. J. CORP. L. 715, 727 (2000).

⁴⁸Symposium, *supra* note 47 at para. 11.

⁴⁹21 U.S.C.A. §360c (West 2003).

Any device intended for human use which was not introduced or delivered for introduction into interstate commerce for commercial distribution before the date of the enactment of this section [enacted May 28, 1976] is classified in class III unless (A) the device

(i) is within a type of device (I) which was introduced or delivered for introduction into interstate commerce for commercial distribution before such date and which is to be classified pursuant to subsection (b), or (II) which was not so introduced or delivered before such date and has been classified in class I or II, and

(ii) is substantially equivalent to another device within such type, or

(B) the Secretary in response to a petition. . . has classified such device in class I or II. *Id.* § 360c (f).

⁵⁰Smith, *supra* note 46 at 87.

⁵¹21 C.F.R. § 56 (2003).

⁵²21 C.F.R. § 812 (2003).

⁵³21 C.F.R. § 312 (2003).

⁵⁴Symposium, *supra* note 47 at para. 8.

different (e.g., in cost recovery and device risk assessment areas), these applications are functionally equivalent and are subject to comparable safety and efficacy standards.⁵⁵ Both IND and IDE applications “include a description of (1) the product and manufacturing processes and methods sufficient to allow an evaluation of product safety and (2) preclinical studies that were appropriately designed to assess risks and potential benefits of the product.”⁵⁶

Clinical studies are divided in three steps or phases. Phase 1 trials are performed in order to determine the feasibility of a product.⁵⁷ Phase 2 trials are used to investigate proper and safe dosing and potential efficacy.⁵⁸ Finally, phase 3 trials are performed to support a determination regarding safety and efficacy and lead to an application to FDA for premarket clearance of a product.⁵⁹

The entity responsible for the clinical investigation (the sponsor) of a “non-significant risk” device may proceed with clinical studies under an “abbreviated IDE.”⁶⁰ This means that the sponsor is only required to have Institutional Review Board approval and informed consent, and not FDA approval of an IDE.⁶¹

A sponsor of a medical device intended to treat a disease or condition that affects fewer than 4,000 people in the United States can obtain a “Humanitarian Device Exemption” (HDE) and will not be required to demonstrate the effectiveness of such a device to obtain premarket clearance.⁶² However, if the amount to be charged for the device is greater than \$250, an HDE applicant must provide a report by a certified public accountant verifying that this amount is not greater than the cost of research, development, fabrication and distribution of the product.⁶³

⁵⁵Kiki B. Hellman, et al., *Regulatory Considerations* in PRINCIPLES OF TISSUE ENGINEERING 917 (Robert P. Lanza, et. al., eds., 2nd ed.2000).

⁵⁶*Id.*

⁵⁷*Id.* at 918.

⁵⁸*Id.*

⁵⁹*Id.*

⁶⁰Symposium, *supra* note 47 at para. 9.

⁶¹*Id.*

⁶²Smith, *supra* note 46 at 84, and 21 U.S.C.A. § 360j(m) (West 2003).

⁶³PARISIAN, *supra* note 19 at 479.

The PHSA requires licensed biological products to be “safe, pure, and potent” and to be manufactured in facilities designed that ensure those qualities.⁶⁴ Additionally, the FDA Modernization Act of 1997 (FDAMA) amended the PHSA to subject biological products to the drug provisions of the FD&CA and all applicable regulations.⁶⁵ The sponsor of a biological product must submit a “Biologics License Application” (BLA) in order to show that their products meet the requirements established by the PHSA.⁶⁶ The sponsor of a biological product must apply for FDA clearance of an IND or, in the case of biological devices, an IDE, in order to conduct clinical trials for receiving premarket approval. Sponsors of prescription drugs and biological products that treat serious or life-threatening illnesses and indicate early favorable outcomes that are likely to predict clinical benefit may apply for “accelerated” or early approval to products.⁶⁷

Needless to say, the current process of developing and bringing “new drugs” (including new biological products) to the market can be very tedious, long, and expensive. Not only is the process for FDA evaluation of these applications a concern, but also the design and implementation of clinical trials are time consuming and require a vast amount of resources.⁶⁸

In addition to the above requirements, all manufacturers of biological products and medical devices must comply with applicable Good Manufacturing Practices, also known as Quality Systems regulations.⁶⁹

A. FDA Regulation of Human Tissue Intended for Transplantation

FDA has recently created a regulatory scheme for human tissue by relying on its authority “to prevent the

⁶⁴42 U.S.C.A. § 262 (West 2003).

⁶⁵FDA Modernization Act of 1997 (FDAMA), (codified at 42 U.S.C.A. §262 (West 2003)).

⁶⁶64 Fed. Reg. 56441.

⁶⁷Final Regulations for Accelerated Approval, 57 Fed. Reg. 5842 (Dec. 11, 1992).

⁶⁸Richard A. Merrill, *Human Tissues and Reproductive Cloning: New Technologies Challenge FDA*, 3 HOUS. J. HEALTH L. & POL’Y 1 (2002).

⁶⁹Smith, *supra* note 46 at 87-88.

introduction, transmission, or spread of communicable diseases” provided by Section 361 of the PHSA.⁷⁰ The agency’s approach to regulation of cellular and tissue-based products was designed in order to prevent use of contaminated tissues with potential to transmit infectious diseases such as AIDS and hepatitis, prevent improper handling or processing that might contaminate or damage tissues, and ensure that clinical safety and effectiveness are demonstrated in the use of all tissues. All human tissue and cell product manufacturers are required to register their establishments and list their products with CBER, regardless of whether the products are regulated as devices or biologics. Following is an excerpt from CBER’s website summarizing the center’s jurisdiction over a limited number of human tissue products, excluding vascularized organs:

... (CBER) currently regulates under 21 CFR Part 1270 human tissue intended for transplantation that is recovered, processed, stored, or distributed by methods that do not change tissue function or characteristics and that is not currently regulated as a human drug, biological product, or medical device. Examples of such tissues are bone, skin, corneas, ligament and tendon. CBER does not regulate vascularized human organ transplants such as kidney, liver, heart, lung or pancreas. The federal Health Resources Services Administration (HRSA) provides oversight and funding support for the nation’s organ procurement allocation and transplantation system, coordinates national organ and tissue donation activities, funds research to learn more about what works to increase donation, and administers the national bone marrow registry program.⁷¹

FDA is constantly criticized for delaying the regulation of organ transplants because many deaths and serious infections have been traced to either contaminated or infected tissues.⁷²

B. Xenotransplantation

CBER also regulates xenotransplantation, which is “any procedure that involves the transplantation, implantation, or infusion into a human recipient of either (a) live cells, tissues, or organs from a nonhuman animal source, or (b) human body fluids, cells, tissues or organs that have had ex vivo contact with live

⁷⁰ 42 U.S.C.A. § 264 (West 2003), See <http://www.fda.gov/cber/tiss.htm>.

⁷² See Robert Pear, *Washington: Report Faults F.D.A. on Tissue Implants*, NY TIMES May 14, 2003.

nonhuman animal cells, tissues or organs.”⁷³ Interest in xenotransplants has dramatically increased due to the short supply and high demand for human organs. These tissues are used experimentally to treat certain diseases such as liver failure and diabetes when human materials are not usually available. Despite their potential to satisfy the high demand for functional organs, the widespread use of these tissues raises public health concerns “regarding the potential transmission of diseases to recipients, their close contacts, and the general human population,” due to certain infectious agents that may not be readily identifiable before the procedure.⁷⁴ An additional public health concern is the potential for cross-species infection by retroviruses which may be latent and lead to disease years after infection.⁷⁵

⁷³ See <http://www.fda.gov/cber/xap/xap.htm>.

⁷⁴ *Id.*

⁷⁵ *Id.*

IV. Tissue-Engineered Replacement Parts

Tissue Engineering is “an interdisciplinary field that applies the principles of engineering and the life sciences toward the development of biological substitutes that restore, maintain, or improve tissue function.”⁷⁶ The main goal in this field is the creation of biologically functional human tissues and organs in the laboratory that can meet the needs of each individual patient and eliminate or reduce the risks associated with conventional replacement therapies, such as transplants and artificial organs.

The field of tissue engineering was born with the use of bioactive materials designed to interact with the body to encourage tissue repair.⁷⁷ Many of the advances in this field have occurred over the past decade, largely by physicians who are keenly aware of the scarcity of transplant tissue.⁷⁸ Tissue engineering is growing at a steady rate since its inception, attracting the interests of academia, industries, government, and the public at large.

The principles of tissue engineering are being applied to virtually every organ system in the body. Tissue engineers have successfully created certain human tissues in the laboratory, including skin, bone, and cartilage. They are also working on the creation of three-dimensional organs. Moreover, it is believed that in a nearby future it will be possible to create entire body parts such as hands and arms in the laboratory.⁷⁹ Nevertheless, there are certain technical and regulatory challenges that need to be overcome before we can have “off-the shelf” or “made to order” replacement parts for our bodies. First, each particular component of a tissue-engineered product must be designed, created, and assembled in a way that can replace all the biological functions of a particular organ. Second, tissue engineered products must receive FDA approval before they enter the U.S. market. As discussed below, only a few engineered tissues such as skin and cartilage have successfully overcome both technical and regulatory challenges.

⁷⁶Langer, *supra* note 6.

⁷⁷Bonassar, *supra* note 25 at 297.

⁷⁸*Id.*

⁷⁹Robert Langer and Joseph P. Vacanti, *Artificial Organs: Engineering Human Tissue is the Natural Successor to Treatments for Injury and Disease, But the Engineers will be the Body's Own Cells* SCI. 56, 58 (1999).

A. General Components of Current Tissue-Engineered Products

Tissue-engineered medical products (TEMPs) may be derived from a wide range of sources, such as human tissues or organs (e.g. autologous or allogeneic tissues), animal tissues or organs (e.g., transgenic animals or xenotransplants); and processed, selected, or expanded human or other mammalian cells (e.g., stem/progenitor cells, genetic and somatic cellular therapies), in combination with or without biomaterials. In addition, totally synthetic materials of biomimetic design may also be considered tissue-engineered.”⁸⁰ Following is a brief discussion about the components of tissue engineered products that have entered the U.S. market, as well as some of the technical, ethical, and regulatory issues associated with them.

1. Cells

Most of the complications associated with allografts and xenografts would be greatly diminished with tissue-engineered products derived from a patient’s own cells. Nevertheless, because of the technical difficulties associated with the isolation, manipulation, and stimulation of growth in already differentiated cells, most tissue engineered constructs are currently derived from neonatal foreskin cells and stem cells. While implants derived from these cells are not rejected because they are “immunologically inert” to the host. Nevertheless, a problem arises because these cells may allow for the transmission of diseases, they must be screened thoroughly.

Some FDA-approved tissue-engineered skin products such as TransCyte and Apligraf are comprised of dermal cells (fibroblasts) isolated from newborn human foreskins obtained through circumcision. These cells-which have not fully developed identifying proteins-are used in order to avoid rejection of the engineered tissue by the host. They also have a large capacity for replication. For example, one foreskin is said to be able to

⁸⁰Hellman, *supra* note 56 at 916.

“produce enough skin to cover six football fields.”⁸¹ However, in addition to the possibility of transmitting diseases through these cells, there is the concern that their use will promote male circumcision. Certain groups are opposed to male circumcision due to its painful nature and the probability of accidents resulting in genital mutilation.⁸²

Embryonic stem cells are another source for tissue-engineered constructs. These are undifferentiated cells with the potential to produce many cell types and to form various types of tissues through mitosis (multiplication) and differentiation (specialization).⁸³ Nevertheless, there is strong opposition against embryonic stem cell research because the procedure by which these cells collected results in the destruction of an embryo that has been either fertilized in vitro or aborted. In 2001, President George Bush limited federal funding to existing stem cell lines derived from already destroyed embryos, and prohibited federal support to the creation of any new lines.

Adult stem cells are being considered as an alternative to embryonic stem cells. Recent research has shown the possibility of cell “reprogramming,” which allows some adult stem cells to take on the characteristics of the tissue to which they are transferred to.⁸⁴ Adult stem cell research eliminates the ethical baggage associated with embryonic stem cell research.⁸⁵ However, most of their properties are currently unknown. Finally, there are a number of technical challenges in the manipulation of stem cells that need to be overcome. According to Joseph P. Vacanti and Robert Langer, pioneers in the field of tissue engineering: “a critical issue for the future, from a tissue-engineering standpoint, is to learn how to control the permanent differentiation of stem-cell populations into the desired cell types, whether we need cartilage, bone, liver, or some

⁸¹Gail Naughton, *The Advanced Tissue Sciences Story*, SCI. AM., April 1999 at 85.

⁸²FDA CDRH General and Plastic Surgery Devices Panel, January 29, 1998, 43-47 transcript available at <http://www.fda.gov>.

⁸³William D. Niemi, *Overview: Stem Cells from a Biological Perspective: What they are, where they are found, and what can be done with them*, 65 ALB. L. REV. 587, 588 (2002).

⁸⁴*Id.* at 590.

⁸⁵For an example of arguments against embryonic stem cell research and in favor of adult stem cell research, see Eugene Tarne, *Verbatim: A Review of the National Institute of Health’s “Guidelines for Research Using Human Pluripotent Stem Cells*, 17 ISSUES L. & MED. 293-307 (2002).

other cell type.”⁸⁶ These challenges will be surpassed as research continues, either through government or private funding. For example, in February of 2003 researchers at the Technion-Israel Institute of Technology succeeded in generating human heart tissue from embryonic stem cells.⁸⁷

2. Biomaterials

In general, “biomaterials are substances other than food or drugs contained in therapeutic or diagnostic systems that are in contact with tissue or biological fluids.”⁸⁸ Many of them were not originally designed for clinical use, but were “off-the-shelf” materials that clinicians found useful in solving a problem.⁸⁹ For example, the polymers initially used in vascular grafts were derived from textiles, and the materials used for artificial hearts were originally based on commercial-grade polyurethanes.⁹⁰ These materials allowed serious medical problems to be addressed, but also introduced complications such as clot formation (from blood-material and tissue-material interactions), thrombosis, countless injuries, and toxic effects. These complications have resulted in multi-million dollar lawsuits against suppliers of biomaterials. Because concerns about the costs of litigation may deter the production of biomaterials, Congress enacted the Biomaterials Access Assurance Act (BAAA) in 1998.⁹¹ This Act shields biomaterials suppliers from tort liability in order to ensure a “continued supply of raw materials and component parts...necessary for the invention, development, and maintenance” of life-saving or life-enhancing medical devices.⁹² Because the BAAA is relatively recent, its effects in the biomaterials industry and products liability litigation-an area of authority

⁸⁶Vacanti, *supra* note 7 at 33.

⁸⁷*Human Heart Tissue Generated from Embryonic Stem Cells*, STEM CELL WEEK, Feb. 3, 2003, available at 2003 WL 8946790.

⁸⁸Nicholas A. Peppas and Robert Langer, *New Challenges in Biomaterials*, 263 SCI. 1715 (1994). “[Biomaterials] are used in many pharmaceutical preparations- for example, as coatings for tablets or capsules or as components of transdermal patches. They play a central role in extracorporeal devices, from contact lenses to kidney dialyzers, and are essential components of implants, from vascular grafts to cardiac pacemakers.” *Id.*

⁸⁹*Id.*

⁹⁰*Id.*

⁹¹The Biomaterials Access Assurance Act of 1998, Pub. L. No. 105-230, 112 Stat. 1519 (codified at 21 U.S.C.A. §§ 1601-1606 (West 2003)).

⁹²21 U.S.C.A. § 1601 (West 2003).

traditionally reserved to state tort law according to notions of federalism and the Tenth Amendment—are still unknown.⁹³

Currently, the field of biomaterials encompasses the study of materials used in the body and the interactions between them and their host.⁹⁴ Many biomaterials used in tissue-engineering are biodegradable (i.e., absorbable by the body) and serve as “temporary scaffolds” for cells to grow in. These “scaffolds” must be designed in a way that resembles natural tissues and allows for the exchange of nutrients and waste products.⁹⁵ Additionally, they must degrade on time to be replaced by growing tissues.

Biomaterials may be natural or synthetic in nature, or a combination of both. The benefits of natural biomaterials are countless. For example, their use in implants may avoid secondary effects related to synthetic materials. Additionally, wounds treated with natural biomaterials such as collagen have been shown to heal remarkably.⁹⁶ Nevertheless, the use of natural biomaterials from donors other than the end recipient may produce allergies in the donor⁹⁷ or result in the transmission of diseases. “The advantage of synthetic materials is that their strength, speed of degradation, microstructure and permeability can be controlled during production; natural materials, however, are usually easier for cells to stick to.”⁹⁸ A synthetic biomaterial should degrade into nontoxic components that can be easily eliminated from the body.

V. FDA Regulation of Tissue-Engineered Medical Products

FDA established an InterCenter Tissue Engineering Working Group (TEWG) in July, 1994 to identify and

⁹³See James D. Kerouac, *A Critical Analysis of the Biomaterials Access Assurance Act of 1998 as Federal Tort Reform Policy*, 7 B.U. J. SCI. & TECH. 327 (2001) and Anne Marie Murphy, *The Biomaterials Access Assurance Act of 1998 and Supplier Liability: Who You Gonna Sue?* 25 DEL. J. CORP. L. 715 (2000).

⁹⁴Bonassar, *supra* note 25 at 297.

⁹⁵T. M. Freyman, et al., *Cellular Materials as Porous Scaffolds for Tissue Engineering*, 46 PROGRESS IN MATERIALS SCI. 273, 274 (2001). “Formation of implanted tissue is greatly influenced by the composition, architecture, and three-dimensional environment of the scaffold, and biocompatibility of the biomaterial.” Mrunal S. Chapekar, *Tissue Engineering: Challenges and Opportunities* 617, 618 (Chemistry and Life Sciences Office, National Institute of Standards and Technology, U.S. Department of Commerce, MD 20899. June, 2000).

⁹⁶See Freyman, *supra* note 96 at 277, concluding that the use of a collagen matrix reduces scar formation during the healing process and showing a photograph comparing healing with and without a collagen matrix.

⁹⁷For example, certain FDA approved tissue-engineered products are not recommended for patients with known allergies to bovine products.

⁹⁸Robert S. Langer, and Joseph P. Vacanti, *Tissue Engineering: The Challenges Ahead*, SCI. AM, April 1999 at 88

address the emerging scientific and science-based regulatory issues of TEMPs.⁹⁹ This group is comprised by staff from five participating FDA centers, CBER, CDER, CDRH, the Center for Food Safety and Applied Nutrition (CFSAN), the Center for Veterinary Medicine (CVM) and certain FDA offices.¹⁰⁰ This group facilitates intercenter communication and cooperation among FDA personnel in order to promote regulatory consistency for TEMPs.¹⁰¹ The TEWG and its members are participating in the development of voluntary consensus standards for various aspects of TEMPs through the American Society for Testing and Materials (ASTM), “a not-for profit organization which provides a forum for producers, users, ultimate consumers, and those having a general interest to meet on common ground and write standards for materials, products, systems and services.”¹⁰² Both FDA and ASTM are making a concerted effort to establish standards and guidelines for the entire field of tissue-engineered medical products (TEMPS).¹⁰³ Historically, ASTM’s Committee F-04 has undertaken responsibility for the development of standards for medical devices.¹⁰⁴ Although the ASTM process is voluntary and does not bind either the FDA or any manufacturer, FDA frequently refers to ASTM standards in its process of evaluation of investigational therapies.¹⁰⁵

A. FDA-Approved Tissue-Engineered Products

Most FDA-approved tissue-engineered products are biologically active wound dressings regulated as devices.¹⁰⁶ The first biologically based wound dressings approved by the FDA were Original Biobrane (Blue

⁹⁹Hellman, *supra* note 56 at 921.

¹⁰⁰*Id.*

¹⁰¹*Id.*

¹⁰²Steven T. Boyce, *Regulatory Issues and Standardization*, in *METHODS OF TISSUE ENGINEERING* 13 (Anthony Atala and Robert P. Lanza, eds. 2002).

¹⁰³See <http://www.fda.gov>, and <http://www.astm.org>.

¹⁰⁴Boyce, *supra* note 103.

¹⁰⁵*Id.*

¹⁰⁶FDA issued a draft guidance for the development of products intended for the treatment of chronic cutaneous ulcer and burn wounds with recommendations about labeling claims, outcome measures, and trial design, as well as special considerations for preclinical development. See *FDA Draft Guidance for Industry-Chronic Cutaneous Ulcer and Burn Wounds: Developing Products for Treatment*, June 1st, 2000 available at <http://www.fda.gov/cder/guidance/3226dft.html>.

Label) (“Biobrane”), manufactured by Bertek Pharmaceuticals, and Integra® Dermal Regeneration Template (“Integra”), manufactured by Integra Life Sciences Corp.¹⁰⁷ Both products are regulated as devices, although they are a combination of synthetic materials and animal tissue products.

Biobrane was approved in 1989 as a “temporary covering of full-thickness burn wounds until autografting is clinically appropriate.”¹⁰⁸ It consists of a silicone film and nylon fabric a knitted nylon fabric coated with a protein (gelatin) derived from pig tissue.¹⁰⁹ The gelatin interacts with clotting factors in the wound and the dressing remains in place until the wound heals or autografting becomes possible.¹¹⁰

1. Application of Tissue-Engineered Skin to Burn Wounds

Every year, 45,000 Americans are hospitalized due to burns arising from fire, contact with electricity, and chemicals or hot liquids and substances among others.¹¹¹ Unfortunately, about ten percent of these victims are fatally lost, sometimes because their wounds allow for massive loss of fluids or infection.¹¹² Covering burn wounds quickly with temporary skin substitutes can help prevent these complications and minimize scarring and trauma.¹¹³

Integra¹¹⁴ was approved in 1996 for the treatment of severe burns.¹¹⁵ It is a membrane consisting of a porous lattice of cross-linked collagen fibers as a dermal layer, and a synthetic, epidermal layer.¹¹⁶ The collagen

¹⁰⁷Linda Bren, *Helping Wounds Heal*, FDA CONSUMER MAG. 4, May-June 2002 available at http://www.fda.gov/fdac/features/2002/302_heal.html.

¹⁰⁸FDA Center for Devices and Radiological Health 1989’s *Significant New Devices*, available at <http://www.fda.gov/bbs/topics/ANSWERS/ANS00102.html>.

¹⁰⁹Bren, *supra* note 108, and Caroline J. Strange, *Second Skins* (1997), available at http://www.fda.gov/fdac/features/1997/197_skin.html.

¹¹⁰*Id.*

¹¹¹American Burn Association, *Burn Incidence in the US: 2000 Fact Sheet*, available at <http://www.ameriburn.org/pub/Burn%20Incidence%20Fact%20Sheet.html>.

¹¹²*Id.*

¹¹³FDA Consumer Updates, July-August 1997, available at http://www.fda.gov/fdac/departs/1997/597_upd.html.

¹¹⁴This product’s original trade name was “Artificial Skin.” In April, 2001 the FDA granted a premarket approval for changing its name to “INTEGRA® Dermal Regeneration Template. *CDRH PMA Final Decisions Rendered for April 2001*, available at <http://www.fda.gov/cdrh/pma/pmaapr01.html>

¹¹⁵*CDRH PMA Final Decisions Rendered for March, 1996*, available at <http://www.fda.gov/cdrh/pmamar96.html>.

¹¹⁶Strange, *supra* note 110 at 3.

fibers in the dermal layer are purified from bovine tendons and chondroitin sulfate (a type of large carbohydrate extracted from shark cartilage). This layer acts as a biodegradable template that helps organize tissue regeneration.¹¹⁷ It is slowly degraded and replaced with authentic human collagen synthesized by cells migrating into the lattice from surrounding healthy tissue as well as other types of cells, blood, and lymph vessels.¹¹⁸ The epidermal (outer) layer is an elastic silicon membrane which provides a moisture barrier, functionally replacing the epidermis. The outer membrane is removed and replaced with very thin epidermal transplant after the dermal layer repairs itself.

Soon after receiving FDA approval, Integra was first applied with remarkable success on a 68-year-old Northern California man who suffered third-degree burns when he dropped his cigarette and his pants leg caught fire.¹¹⁹ One year later, it was used in an attempt to save 61-year-old Betty Shabazz, the widow of Malcolm X.¹²⁰ Mrs. Shabazz was the victim of a fire set in her New York apartment by her twelve year-old grandson. She suffered third-degree burns over eighty percent of her body, and was hospitalized in critical condition at the Jacobi Medical Center in Bronx, NY.¹²¹ Because burn skin is prone to infection and causes massive loss of fluids, three days after the fire surgeons removed twenty percent of her damaged skin and replaced it with Integra.¹²² However, Mrs. Shabazz succumbed to her injuries about three weeks later. Statistically, patients in her condition have greater than ninety percent mortality rate.¹²³

Last year, Integra was also approved for use in the treatment of “disabling” scars that result from severe burns.¹²⁴ It has an approved expiration date of twenty-four months.¹²⁵

¹¹⁷ *Id.*

¹¹⁸ *Id.*

¹¹⁹ *Id.* at 1.

¹²⁰ Gary Stix, *Growing a New Field: Tissue Engineering Comes into its Own*, SCI. AM. October 1997 at 15.

¹²¹ *Id.*

¹²² Beth Harpazz, *Shabazz Receiving Artificial Skin*, REC., June 5, 1997 at A06.

¹²³ *Id.*

¹²⁴ *New Device Approval: Integra-Dermal Regeneration Template- P 900033/S008*, FDA CDRH CONSUMER INFO., available at <http://www.fda.gov/cdrh/mda/docs/p900033S008.html>. “These scars have the effect of immobilizing or “freezing” the skin, preventing limbs from moving or the body part from further developing.” *FDA Approves Reconstructive Surgery Product for Patients with Severe Scarring*. FDA TALK PAPER available at <http://www.fda.gov/bbs/topics/ANSWERS/2002/ANS01148.html>.

¹²⁵ CDRH PMA Final Decisions Rendered for August, 1997. <http://www.fda.gov/cdrh/pmaaug97.html>

In 1997, TransCyte™ (“TransCyte”)¹²⁶ became “the first wound covering made with human cells. . . approved by FDA to temporarily cover severe burn wounds until a patient’s own skin can be transplanted.”¹²⁷ Its approval was based on a recommendation from the General and Plastic Surgery Panel of the agency’s Medical Devices Advisory Committee.¹²⁸ TransCyte was initially approved for the treatment of full-thickness (third-degree) burns.¹²⁹ It was approved a couple of months later for the treatment of partial-thickness (second-degree) burns as well.¹³⁰

TransCyte “covers and protects burns, helping to minimize infections and retain fluids until a sufficient amount of the patient’s own skin is available for autologous grafting.”¹³¹ It consists of dermal cells (fibroblasts) obtained from newborn human foreskins and a synthetic, epidermal layer. These cells are “alive” until frozen for shipment and use.¹³² TransCyte is removed “when the patient’s own skin is ready to be grafted, usually in seven to fourteen days.”¹³³ It has an expiration date of twenty months and may be stored by the end user at temperatures between minus seventy and minus twenty degrees Celsius.¹³⁴

OrCel™ (Bilayered Cellular Matrix) (“OrCel”), approved in 2001,¹³⁵ “is an absorbable cellular matrix, made of collagen, in which human skin cells have been cultured.”¹³⁶ This product manufactured by Ortec

¹²⁶This product’s original trade name was Dermagraft Temporary Covering (Dermagraft-TC™). In August, 1998 the FDA granted a premarket approval for changing its name to “TransCyte” <http://www.fda.gov/cdrh/pma/pmaa098.html>.

¹²⁷FDA Consumer Updates, July-August 1997 available at http://www.fda.gov/fdac/departs/1997/597_upd.html.

¹²⁸*Id.*

¹²⁹“The device is indicated for use as a temporary wound covering for surgically-excised full-thickness and partial-thickness dermal burn wounds in patients who require such a covering prior to autograft placement.” *CDRH PMA Final Decisions Rendered for March 1997*, available at <http://www.fda.gov/cdrh/pmamar97.html>. See Naughton, *supra* note 82 at 84.

¹³⁰*CDRH Final Decisions Rendered for October, 1997*, available at <http://www.fda.gov/cdrh/pmaoct97.html>. See Naughton, *supra* note 82 at 84.

¹³¹*Tissue Engineering: Despite Technical and Regulatory Challenges, the Prospects for Tissue Engineering are Good*. 18 NATURE BIOTECHNOLOGY IT56, IT47 (2000).

¹³²Naughton, *supra* note 82.

¹³³FDA Consumer Updates, *supra* note 128.

¹³⁴*CDRH PMA Final Decisions Rendered for March 2000*, available at <http://www.fda.gov/cdrh/pma/pmamar00.html>.

¹³⁵*CDRH PMA Final Decisions Rendered for August, 2001*, available at <http://www.fda.gov/cdrh/pma/pmaa001.html>. A copy of OrCel’s approval letter and summary of its safety and effectiveness, labeling, and other consumer information, is available at <http://www.fda.gov/cdrh/pdf/p010016.html>

¹³⁶*New Wound Dressing for Burn Patients*, FDA PATIENT SAFETY NEWS, April 2002 available at <http://www.fda.gov/cdrh/psn/show3.html>. In January 17, 2002 FDA granted a premarket approval for use of cell line FS-183 in the commercial manufacture of OrCel™ Bilayered Cellular Matrix. *CDRH Final Decisions Rendered for January 2002*, available at <http://www.fda.gov/cdrh/pma/pmaj02.html>.

International Inc. is not used on the burn itself, but rather on the site where some of the patient's healthy skin was removed for grafting to the burn site (a technique called split thickness skin grafting).¹³⁷ The dressing is gradually absorbed during the healing process.¹³⁸

¹³⁷*New Wound Dressing for Burn Patients*, *supra* note 37.

¹³⁸*Id.*

2. Application of Tissue-Engineered Skin to Chronic Wounds

Lower extremity ulcers include venous and diabetic foot ulcers, both of which result in localized tissue death. Both are major health problems because of their high prevalence and elevated health care costs associated with them. The incidence of chronic wounds is expected to continue rising as the general population ages. Venous insufficiency is the most common cause of lower leg ulcers. Approximately seven million Americans have venous insufficiency, and about one million of them develop venous leg ulcers.¹³⁹ Patients with venous leg ulcers suffer from abnormally sustained elevation of the venous pressure upon ambulation, and commonly report swelling and aching of the legs.¹⁴⁰

According to the American Diabetes Association, approximately 17 million people in the United States (about six percent of the total population) are afflicted with diabetes.¹⁴¹ Diabetes is a disease in which the body does not produce or properly use insulin, a hormone needed to convert sugar, starches, and other foods into energy needed for daily life.¹⁴² Diabetes may result in complications such as heart disease, kidney disease, blindness, and foot ulcers.¹⁴³ Diabetic foot ulcers are often the result of nerve damage or poor blood circulation in the feet.¹⁴⁴ About fifteen percent of diabetics develop foot ulcers.¹⁴⁵ If not properly cared for, foot ulcers can result in lower-limb amputation. More than sixty percent of nontraumatic lower-limb amputations in the United States occur among people with diabetes.¹⁴⁶ Additionally, about 82,000 nontraumatic lower-limb amputations were performed each year among people with diabetes from 1997 to 1999.¹⁴⁷

In 1998 the General and Plastic Surgery Devices Advisory Panel to the FDA recommended “unconditional ap-

¹³⁹Tami de Araujo, *Managing the Patient with Venous Ulcers*, 138 ANN INTERN MEDICINE (138) 326 (2003).

¹⁴⁰*Id.*

¹⁴¹American Diabetes Association, *National Diabetes Fact Sheet*, available at <http://www.diabetes.org>.

¹⁴²*Id.*

¹⁴³*Id.*

¹⁴⁴*Id.*

¹⁴⁵Naughton, *supra* note 82.

¹⁴⁶American Diabetes Association, *supra* note 142.

¹⁴⁷*Id.*

proval” of Apligraf (Gratskin) Human Skin Equivalent (“Apligraf”) for the treatment of venous leg ulcers.¹⁴⁸ Apligraf, a two-layer skin substitute manufactured by Organogenesis, became “the first manufactured living human organ recommended for approval by an advisory panel to the FDA.”¹⁴⁹ Its upper layer consists of keratinocytes, the dominant cell type in the epidermis, and its lower layer consists of collagen and fibroblasts, the main constituents of the dermis.¹⁵⁰ The cells in Apligraf, like TransCyte, were originally derived from infant foreskin. Organogenesis, Inc. has subsequently obtained various premarket approvals to introduce new cell strains in Apligraf’s manufacture.¹⁵¹ Although Apligraf is “alive,” it is regulated by the FDA as a device.¹⁵²

Apligraf was initially approved “for the treatment of non-infected partial and full-thickness skin ulcers due to venous insufficiency of greater than 1 month duration and which have not adequately responded to conventional ulcer therapy.”¹⁵³ Subsequently, it was granted approval for use in the treatment of diabetic foot ulcers “greater than three weeks duration which have not adequately responded to conventional . . . therapy and which extend through the dermis but without tendon, muscle, capsule or bone exposure.”¹⁵⁴

Dermagraft, like TransCyte, is manufactured by Advanced Tissue Sciences. “The key difference between the two products is that Dermagraft remains a living tissue, so it can be used in instances in which new skin must be induced to grow, such as diabetic foot ulcers or bed sores.”¹⁵⁵ It was approved in 2001 “for use in the treatment of full-thickness diabetic foot ulcers greater than six weeks duration which extend through the dermis, but without tendon, muscle, joint capsule or bone exposure. . . in conjunction with standard wound care regimens and in patients that have adequate blood supply to the involved foot.”¹⁵⁶

¹⁴⁸ *Tissue Engineering: Despite Technical and Regulatory Challenges, the Prospects for Tissue Engineering are Good*, *supra* note 132.

¹⁴⁹ *Id.*

¹⁵⁰ Strange, *supra* note 110 at 5.

¹⁵¹ See <http://www.fda.gov>.

¹⁵² Nancy Parenteau, *Skin: The First Tissue Engineered Products: The Organogenesis Story*, SCI. AM. April 1999 at 84.

¹⁵³ CDRH PMA Final Decisions Rendered for May 1998, available at <http://www.fda.gov/cdrh/pma/pmamay98.html>.

¹⁵⁴ See CDRH PMA Final Decisions Rendered for July 2000, available at <http://www.fda.gov/cdrh/pma/PMAJUN00.HTML>.

¹⁵⁵ Naughton, *supra* note 82 at 84.

¹⁵⁶ CDRH PMA Final Decisions Rendered for September 2001, available at <http://www.fda.gov/cdrh/pma/pmasep01.html>.

Dermagraft can remain on a shelf up to six months when maintained at a temperature of minus seventy-five degrees Celsius, “a major advantage over similar types of dressings.”¹⁵⁷ However, it is not recommended for use in patients allergic to bovine products, as it may contain trace amounts of bovine proteins.¹⁵⁸

In addition to their application in the treatment of burns and diabetic foot ulcers, tissue-engineered skin substitutes have been approved for other conditions such as Recessive Dystrophic Epidermis Bullosa (RDEB). RDEB is a rare, inherited disease afflicting children in which blisters and sores appear on fingers and toes, sometimes producing scarring that makes them grow together.¹⁵⁹ Afflicted hands are traditionally rebuilt by using pieces of the child’s own skin for grafts.¹⁶⁰ These grafts may be replaced by tissue engineered skin, thus reducing the number and size of surgical wounds on the patient.¹⁶¹

In 2001 the FDA granted Ortec International, Inc. a humanitarian device exemption to market its Composite Cultured Skin (CCS) for use in patients with Recessive Dystrophic Epidermis Bullosa (RDEB) undergoing hand reconstruction, as well as to cover donor sites created during surgery.¹⁶² CCS is made from human cells from healthy donors grown on a bovine collagen sponge.¹⁶³

3. Additional Applications of Tissue-Engineered Skin

Tissue-engineered skin has proven useful in laboratory testing for certain chemical products. In fact, some of these products have been approved by various federal regulatory agencies for replacing or reducing animal and cadaver skin testing for many cosmetic, cleaning, and petrochemical products. For example, in June, 1994 the U.S. Department of Transportation approved the use of an in vitro laboratory test kit as an alternative

¹⁵⁷ *CDRH Office of Device Evaluation Annual Report, Fiscal Year 2001*, available at <http://www.fda.gov/cdrh>.

¹⁵⁸ *Id.*

¹⁵⁹ *CDRH New Humanitarian Device Approval: Composite Culture Skin-H990013*, Feb 21st, 2001 available at <http://www.fda.gov/cdrh/mda/docs/h990013.html>

¹⁶⁰ *Id.*

¹⁶¹ *Id.*

¹⁶² *Press Release: Ortec Receives FDA Approval to Market its Tissue-Engineered Product for Use in Epidermis Bullosa Patients’ Hand Reconstruction*, CHEMICAL BUS. NEWSBASE, February 28, 2001 and *CDRH New Humanitarian Device Approval Composite Cultured Skin-H90013*, *supra* note 160.

¹⁶³ *CDRH New Humanitarian Device Approval Composite Cultured Skin-H90013*, *id.*

to live animal testing of potentially corrosive material.¹⁶⁴ This test kit, named Skin2, contains living human skin tissue cultured by Advanced Tissue Sciences, Inc.¹⁶⁵ Additionally, the Department and Transportation, the Consumer Safety Commission, and FDA approved the use of Corrositex, a protein membrane that can replace rabbit skin tests with results available in just a few hours at \$100 per test.¹⁶⁶ Traditional testing methods using rabbits can take up to twenty-one days and cost as much as \$1,000 per test.

4. Additional FDA-Approved Tissue-Engineered Products

In addition to tissue-engineered skin, FDA has approved a limited number of tissue-engineered products. For example, the agency granted “accelerated approval”¹⁶⁷ for tissue-engineered product named Carticel in 1997. This product, which “uses a patient’s own cartilage cells in a surgical procedure to repair cartilage damage in the knee,”¹⁶⁸ is regulated as a biological product.¹⁶⁹ Carticel is generally used along with other procedures, such as elimination of the damaged tissue and an extensive rehabilitation program.¹⁷⁰ Additionally, the agency approved two collagen-based surgical mesh devices called FortaGenTM and GraftPatch, manufactured by Organogenesis, Inc.; and Surgisis, manufactured by Cook Biotech, Inc. These products have a variety of applications, such as reinforcement of soft tissue including the abdominal and thoracic wall, reconstruction of the pelvic floor, and reconstructive procedures.¹⁷¹

¹⁶⁴ *Advanced Tissue Sciences, Inc. First to be Granted Regulatory Approval for Human Tissue-Based In Vitro Test Method*. PR NEWswire, June 29, 1994.

¹⁶⁵ *Id.* This product was discontinued in 1996 for financial reasons. *Advanced Tissue Sciences to Discontinue Skin2 Product*, MEDICAL INDUSTRY TODAY, September 17, 1996.

¹⁶⁶ Kathi Keville, *Compassionate Cosmetics: Once an Accepted Part of the Beauty Industry, Animal Testing is Becoming a Thing of the Past*, 64 BETTER NUTRITION 58, June 1st, 2002.

¹⁶⁷ *CDER and CBER Draft Guidance for Industry: Accelerated Approval Products –Submission of Promotional Materials*, March, 1999 available at <http://www.fda.gov/cber/gdlns/accpromdft.pdf>.

¹⁶⁸ *FDA Grants Accelerated Approval to Help Repair Damaged Knee Cartilage* FDA TALK PAPER August 25, 1997, available at <http://www.fda.gov/bbs/topics/ANSWERS/ANS00814.html>.

¹⁶⁹ *CBER 1997 Biological License Application Approvals*, available at <http://www.fda.gov/cber/appr1997/1997lic.html>. Carticel was the first product approved under FDA’s “manipulated autologous structure” (MAS) guidance for industry, which “deals with products comprised of living human cells manipulated outside the body and returned to the patient for structural repair or reconstruction.” *FDA Grants Accelerated Approval to Help Repair Damaged Knee Cartilage*, *supra* note 169.

¹⁷⁰ *Id.*

¹⁷¹ *See* <http://www.fda.gov>.

VI. Discussion

There are many uncertainties regarding the regulation of tissue-engineered constructs and combination products. First, FDA is statutorily required to determine the “primary mode of action” of combination products and classify them as biologics, drugs, or devices. However, the lack of federal guidance about the proper interpretation for this term prompts confusion among both manufacturers and FDA personnel. These uncertainties stem from differences in the regulatory pathways for biologics, drugs and devices, which in turn dictate the length and costs of the premarket approval process. Thus, a manufacturer may prefer to have his product classified as a device rather than a biologic if that determination can save him time, effort, and money.

In June 2002, FDA held a public hearing to discuss the jurisdictional classification, assignment, and premarket review of combination products consisting of living human cells in combination with a device matrix; with focus on products intended for wound healing and skin regeneration or replacement.¹⁷² Biologically active wound dressings and tissue-engineered skin are regulated as devices, although the statutory definition for this category excludes products that achieve their primary intended purposes through either “chemical action within or on the body,” or metabolization.¹⁷³

FDA is considering regulating combination products as biologics and transferring their jurisdiction from CDRH to CBER. The agency already communicated to the European Commission that European Union device authorities “should apply drug laws to human tissue-engineered products, including devices, rather than draft a separate law.”¹⁷⁴

Manufacturers of tissue-engineered constructs strongly oppose to the jurisdictional change of their products, perhaps because only devices are insulated from product liability litigation. Section 521 of the FD&CA

¹⁷²Combination Products Containing Live Cellular Components, *supra* note 30.

¹⁷³21 U.S.C.A. § 321, *supra* note 14.

¹⁷⁴*FDA Tells E.U. to Regulate Tissue Devices as Drugs*, DEVICES AND DIAGNOSTICS LETTER, Vol. 30 February 10, 2003, *citing* the E.C. consultation paper and summary of comments *available* at http://europa.eu.int/comm/enterprise/medical_devices/consult_tissue_engineer.htm.

expressly preempts state regulation for devices, while no such protection exists for drugs or biologics.¹⁷⁵ Nevertheless, as tissue-engineered constructs become less “structural” and more “functional” in nature, it may become increasingly difficult to grant them approval under the current statutory definition of a device.¹⁷⁶

Differences in the regulatory requirements for drugs, biologics and devices also result in numerous differences among the CDER, CBER, and CDRH; the centers responsible for regulating these products. Both regulatory and organizational differences frequently cause personnel within a particular center to be “only peripherally familiar with another Center’s regulatory authorities and timelines,”¹⁷⁷ and may result in significant delays if a consulting request is sent to the incorrect division or branch.¹⁷⁸ Nevertheless, there are similar practices and a number of common guidance documents between CBER and CDER, especially after the implementation of the Biologics License Application and the FDA Modernization Act of 1997.¹⁷⁹ As shown by the following excerpt from a report about FDA employee perspectives on the regulation of combination products, there are significant differences between these two centers and CDRH.¹⁸⁰

[T]here appears to be a perception among some in CBER and CDER that CDRH does not review submissions “as well” or hold the sponsors to a sufficiently high standard for demonstration of safety and effectiveness. . . Differences in policies and perspectives also complicate the review of combination products. Or example, in reviewing the safety and effectiveness of “fixed-combination prescription drug products” (where two or more drugs are combined in a single dosage form), CDER requires the contribution of each effective ingredient in the combination to be demonstrated. Therefore, CDER participants reported a tendency to apply a similar approach to combinations of drugs and devices or drugs and biologics. In contrast, *CDRH generally reviews the safety and effectiveness of the overall combination product without requiring the contribution of the components to be separately evaluated.*¹⁸¹

¹⁷⁵Symposium, *supra* note 47 at para. 22.

¹⁷⁶Smith, *supra* note 46 at 83.

¹⁷⁷*Regulation of Combination Products: FDA Employee Perspectives*, *supra* note 32 at 7.

¹⁷⁸*Id.* at 5.

¹⁷⁹Malinowski, Michael J. Overview of FDA Regulation of Human Medicinal Products Developed with Biotechnology. Practising Law Institute, Patents, Copyrights, Trademarks and Literary Property Course Handbook Series. PLI Order No. G0-0129 San Francisco, September 19-20 2002. Biotechnology Law 2002: Biotechnology, Patents & Business Strategies 718 PLI/Pat 979. 1-28, p. 4 (2002)

¹⁸⁰*Regulation of Combination Products: FDA Employee Perspectives*, *supra* note 32 at 8.

Uncertainties about FDA regulation of combination products, in addition to the high costs of developing tissue-engineered products and conducting clinical trials needed to obtain FDA approval may cause significant losses for tissue-engineering business enterprises. For example, in 2002 Advanced Tissue Sciences filed for bankruptcy. It is believed that its bioengineered-skin products, though a scientific achievement, were hard to sell in the current cost-conscious environment. An eight-week regimen of Dermagraft replacement skin costs \$4,000 and no major health insurance company agreed to pay for the product.¹⁸² The company lost \$16.3 million for the first six months of 2002.¹⁸³ Additionally, in 1994 it lost \$22.8 million attributed to the high cost of conducting human clinical trials for FDA premarket approval.¹⁸⁴

In addition to the regulatory challenges outlined above, there are still many technical challenges to overcome before we create “off-the-shelf” tissues that represent the translation of scientific discoveries into treatments for millions of patients. These challenges include finding adequate sources of healthy, expandable cells; learning how to regulate cell behavior; establishing a reliable source of biomaterials, optimizing scaffolds; designing bioreactors that mimic conditions inside the human body; maximizing the mechanical properties of tissues as they grow in bioreactors; inducing the proper growth of blood vessels and nerves; and developing new methods of tissue preservation in order to extend their shelf-life.¹⁸⁵ It is also important to develop methods for the prevention of adverse reactions and the rejection of tissue-engineered products once they have been implanted. For example, products such as Dermagraft, CCS, and OrCel are not recommended for use on patients allergic to bovine products or certain antibiotics. Additionally, there is a need to develop objective tests to measure the mechanical properties of tissue-engineered constructs. Finally, there is no consensus about the cosmetic superiority resulting from the application of tissue-engineered constructs over

¹⁸²Denise Gellene, *Advanced Tissue Woes a Blow to Industry*, LA TIMES 1, October 12, 2002.

¹⁸³*Id.*

¹⁸⁴*Have a Heart: Tissue-Engineered Valves may Offer a Transplant Alternative*, SCI. AM. June 1995 at 46.

¹⁸⁵Linda J. Griffith and Gail Naughton, *Tissue Engineering-Current Challenges and Expanding Opportunities*, 295 SCI. 1009 (2002), and Langer, *supra* note 99.

alternate methods of treatment.¹⁸⁶

Tissue-engineered products also share some of the challenges posed by conventional replacement parts for humans. For example, these products may also be subject to human error, poor manufacturing qualities, improper maintenance, and contamination. FDA has protocols for monitoring and addressing each one of these problems with respect to conventional replacement parts, and has already applied some of them to tissue-engineered products. For example, Apligraf and Carticel have been the subject of product recalls. Fifty-eight Apligraf units were recalled in September 1999 due to a packaging error.¹⁸⁷ Additionally, thirty-two Apligraf units were recalled in March 2000¹⁸⁸ and forty-six units in April 2001 due product contamination.¹⁸⁹ Likewise, contaminated Carticel products have been recalled on five different occasions.¹⁹⁰ Despite both technical and regulatory hurdles, tissue-engineered products have the potential for replacing conventional replacement parts for humans. Moreover, these concerns are being addressed by both researchers and federal decision makers, the entities ultimately responsible for bringing tissue-engineered products to the United States market.

¹⁸⁶For a critique about the use of tissue-engineering products in reconstructive surgery, see Vincent R. Hentz and James Chang, *Tissue Engineering for Reconstruction of the Thumb* 344 NEJM 1547 (2001).

¹⁸⁷FDA Enforcement Report, September 1st, 1999, available at <http://www.fda.gov/bbs/topics/ENFORCE/ENF00605.html>.

¹⁸⁸FDA Enforcement Report, March 15, 2000, available at <http://www.fda.gov/bbs/topics/ENFORCE/ENF00633.html>.

¹⁸⁹FDA Enforcement Report, April 11, 2001, available at <http://www.fda.gov/bbs/topics/ENFORCE/2001/ENF00688.html>.

¹⁹⁰These product recalls were published in the FDA Enforcement Reports for the following dates: December 23, 1998 available at <http://www.fda.gov/bbs/topics/ENFORCE/ENF00569.html>; May 19, 1999 available at <http://www.fda.gov/bbs/topics/ENFORCE/ENF00590.html>; August 16, 2000 available at <http://www.fda.gov/bbs/topics/ENFORCE/ENF00655.html>; available at, January 21st, 2001 at <http://www.fda.gov/bbs/topics/ENFORCE/2001/ENF00678.html>; and April 25, 2001, available at <http://www.fda.gov/bbs/topics/ENFORCE/2001/ENF00690.html>.